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TITLE: Exercise to Counteract Loss of Bone and Muscle during Androgen Deprivation Therapy in Men with Prostate Cancer

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14. ABSTRACT

The original objective was to determine whether a 1-year intensive resistance exercise training (RT) program is more effective than a moderate-intensity walking program in ameliorating the effects on body composition of androgen deprivation therapy (ADT) in men with prostate cancer. It was postulated that: 1) RT will attenuate the declines in bone mineral density (BMD) and fat-free mass (FFM) to a greater extent than walking; and 2) both RT and walking will prevent an increase in fat mass. Primary outcomes are lumbar spine BMD and FFM. Secondary outcomes are: total body and hip BMD; fat mass; markers of bone turnover; serum sex hormones; physical functional performance; quality of life, and risk factors for cardiovascular disease (blood lipids, glucose tolerance, arterial stiffness). Because of the inability to enroll the projected number of participants, the study protocol was modified at the time of the 2006 annual IRB review to focus only on the intensive resistance training intervention.

15. SUBJECT TERMS
bone mineral density, osteoporosis, sarcopenia, bone turnover, resistance exercise training

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INTRODUCTION

The original aim of the study was to determine whether a 1-year intensive resistance exercise training (RT) program is more effective than a moderate-intensity walking program in ameliorating the effects on body composition of androgen deprivation therapy (ADT). It was postulated that, in men on ADT for the treatment of prostate cancer: 1) RT will attenuate the declines in bone mineral density (BMD) and fat-free mass (FFM) to a greater extent than walking; and 2) both RT and walking will prevent an increase in fat mass. It was proposed that a total of 40 men would be enrolled and randomized to either the RT or walking exercise programs. Primary outcomes are lumbar spine BMD and FFM**.** Secondary outcomes are: total body and hip BMD; fat mass; markers of bone turnover, to determine whether changes in BMD are the result of changes in bone resorption and/or formation; serum sex hormones, including testosterone, estradiol, estrone, and sex hormone binding globulin; physical functional performance; and quality of life. Local project support will enable additional assessments of risk factors for cardiovascular disease, including blood lipid profile, oral glucose tolerance, and arterial stiffness. These procedures were not included in the original grant application, but were described in the revised protocol that was approved by the local IRB and the HSRRB. Because of the inability to enroll the projected number of participants, the study protocol was modified at the time of the 2006 annual IRB review to focus only on the intensive resistance training intervention, as discussed below.

It was brought to the attention of the PI by e-mail on 6 July 2007 that the annual report for this study was overdue. This was due to a misunderstanding on her part. Because the period of award was extended through 13 August 2008 (no-cost extension), she mistakenly thought the progress report was due 13 August 2007.

BODY

The tasks in the Statement of Work are as follows:

Task 1: Preparation to initiate studies; months 1 – 3

- secure local IRB and HSRRB approval for study
- apply for research support from the General Clinical Research Center (GCRC)
- apply for research support from the Clinical Nutrition Research Unit (CNRU)
- prepare data forms
- prepare data base
- train research staff

Final approval of the protocol by the HSRRB was 8 August 2004. Thereafter, final approvals were obtained from the GCRC and CNRU for local project support. Recruiting efforts began in November 2004. The protocol last underwent local IRB annual renewal in August 2006.

Task 2: Subject recruitment; months 4-21

- enroll 2-3 subjects per month, total of 40
- recruiting lectures at local prostate support group meetings
- meetings with private urology clinic staffs
- interactions with health reporters for local media
- place advertisements on newspaper and radio

A high level of attention was directed to this task in the past year, but enrollment remains below the projected level. Recruitment activities included:

May 2006: An e-mail announcement was placed on the UCDHSC community electronic bulletin board. This generated three calls, one orientation, and one enrollment.

June through August, 2006: Met with the urology groups at area hospitals including the Denver VA Hospital, Swedish Medical Center, Porter Hospital, Presbyterian/St. Luke’s, and St. Anthony's Hospital to discuss our study and distribute recruitment fliers at their practices.

July, October 2006: Included a description of the study in our research group’s quarterly newsletter, which was distributed to more than 1000 former research volunteers.

September, 2006: Presented a research seminar on *Metabolic Consequences of Androgen Deprivation in Prostate Cancer* to the UCDHSC Prostate Cancer Research group. This did not lead directly to any patient referrals.

November 2006: Met with the urology/oncology clinical research coordinators in the UCDHSC Cancer Center to discuss recruitment of clinic patients.

November 2006: Met with a private local urology group, Urology Center of Colorado, that offered to send letters to their patients informing them about our study. We sent over 300 letters to patients. This resulted in 10 calls, 3 orientations, 2 consents and 1 participant who is currently enrolled.

December 2006: Met with office manager of the UCDHSC Urology clinic to arrange to send letters to their patients informing them about our study. We sent over 250 letters to patients in this practice. This interaction resulted in 5 calls, 2 orientations, and 0 consents.

January, 2007: Contacted a local television network that was running a series of reports on prostate cancer to inquire whether a description of the research project could be included in one of the reports. The response was that the anchorman in charge of developing the story would be in contact if it met the needs of the story; no further correspondence was received.

January 2007: Discussed the study and distributed brochures to internists at UCDHSC.

January, April 2007: Included a description of the study in our research group's quarterly newsletter, which was distributed to more than 1000 former research volunteers.

February 2007: Hosted a table and distributed study brochures at the African-American Health and Wellness Fair. This did not lead to any calls of inquiry.

April 2007: Hosted a booth at the 9News Health Fair. These efforts generated 2 calls but no qualifiers.

May 2007: Contacted the president of Progress for Prostate, a Denver-based non-profit organization with a mission to increase prostate cancer awareness and research funding in Colorado. We plan to promote our research activities via the Progress for Prostate website and will take advantage of the organization's associations with local television and print media outlets.

June 2007: Sent copies of study advertisements to the website coordinator for Progress for Prostate.

In summary, 119 men have inquired about the study, 36 of these men attended an orientation session, 33 provided informed consent, and 10 were enrolled in the study; 5 have completed the intervention. Of the 23 who consented but were not enrolled at the time of this report: 1 was in the screening process, 12 dropped out for personal reasons before beginning exercise, 1 was disqualified due to a positive bone scan, 1 was found to have renal disease, 1 began taking glucocorticoids, 2 started bisphosphonate therapy, 1 started estrogen therapy, 2 were unwilling to have hernia repair, 1 was already exercising too much, and 1 had oxygen desaturation during a walk test and never followed through with further evaluation by his primary care provider.

Task 3: Implement resistance exercise ~~and walking exercise~~ programs~~;~~ months 5 - 32

- maintain records of attendance, exercise performance
- routine maintenance of equipment
- track progress of individual participants

This task is progressing, though at a slower rate than projected. Because of the slow recruitment and the approaching end of the award period, the protocol was modified at the last annual IRB review (see discussion following Task 5).

Task 4: Data acquisition and management; months 4 – 32

- schedule all baseline and follow-up testing sessions for all participants
- review all data forms prior to computerization
- enter data into database
- perform routine quality control of database
- track blood samples stored for batch analyses of sex hormones and markers of bone turnover to be performed as participants complete the intervention

This task is progressing as planned, though at a slower rate than projected.

Task 5: Prepare schedule reports; months 1 to 36

- prepare required progress reports
- secure annual IRB (and HSRRB, if necessary) renewal of protocol
- file serious adverse event forms as necessary
- prepare abstracts for presentation

Annual IRB approval was obtained in August 2006. No serious adverse events have occurred. Because of the inability to recruit the targeted number of participants, the decision was made at the time of the IRB renewal to focus the intervention only on the intensive resistance exercise intervention (i.e., discontinue randomization to the walking exercise group). Although this is not an ideal experimental design, the rationale was that it would be better to increase the sample size in the resistance group in the hope of being able to demonstrate significant increases in bone and muscle mass in response to exercise (if they occur), than to distribute the limited number of subjects across two groups and have very little chance of demonstrating differences between the groups in the adaptations to exercise. All updates to the protocol were submitted to Mr. Peter Marshall at Fort Detrick, MD. The last correspondence from Mr. Marshall, stating that he was processing the updated protocol, was received on 29 November 2006.

KEY RESEARCH ACCOMPLISHMENTS

At this stage of the project there are no key accomplishments.

REPORTABLE OUTCOMES

At the stage of the project there are no reportable outcomes.

CONCLUSIONS

Despite vigorous recruitment efforts, we have been unable to enroll the projected number of participants. We remain committed to determining whether an intensive resistance exercise program can generate increases in BMD and fat-free mass in men undergoing ADT. The importance of determining the effectiveness of exercise to counteract some of the effects of ADT has not diminished since we started the project. For example, in 2006 and 2007 alone, there have been numerous published reviews on the devastating effects of ADT on the bone health of men with prostate cancer.[1-13] Recent studies indicate that the rate of decline in BMD increases 5- to 10-fold after the initiation of ADT[14] and that the relative risk of osteoporotic fracture is increased by 30% to 300%.[15-17] In 31 men undergoing ADT who were treated with placebo in a bisphosphonate intervention trial,[18] the lumbar spine T-score decreased from an average of -0.8 to -2.5 after only 3 years; all of the participants were classified as either osteopenic (n=13) or osteoporotic (n=18). Recently, the prevalence of osteoporosis was reported for 390 men with prostate cancer undergoing ADT.[19] The prevalence of osteoporosis increased from 35% in hormone-naïve patients to 43%, 49%, 60%, 66%, and 81% after 2, 4, 6, 8, and 10+ years of ADT, respectively. Although pharmacotherapies that have proven to be effective in preventing fractures in postmenopausal women[20] may also be effective men undergoing ADT,[18,21] such therapies do not ameliorate other consequences of ADT that are likely to increase morbidity and mortality. Specifically, when compared with either healthy men or men with prostate cancer who are *not* on ADT, men with prostate cancer on ADT lose more muscle, gain more fat (particularly in the abdominal region), and become more insulin resistant and glucose intolerant.[14,22-25] It has been reported that the prevalence of the metabolic syndrome in men undergoing ADT is more than 50%.[26] Thus, the metabolic consequences of ADT are likely to increase risk for physical disability, cardiovascular disease, and type 2 diabetes mellitus. Because exercise is the *only* intervention that has the potential to favorably influence *all* of these consequence of ADT and improve survival and quality of life in men with prostate cancer, conducting exercise intervention studies, such as the one in process, is the first step in providing preliminary evidence for the effectiveness of exercise in this population. Although we will not achieve full enrollment and had to modify the protocol as a result of this, we anticipate that important preliminary data will be generated that could stimulate larger clinical trials to fully evaluate this issue. Importantly, a recent study evaluated changes in body composition, muscle strength, and BMD in response to 5 months of resistance training in 10 men with prostate cancer undergoing ADT (i.e., same study design as our modified protocol).[27] There were significant improvements in muscle strength and functional performance. Fat-free mass and BMD were maintained, but did not increase. Because the current ongoing study involves 12 months of resistance, this should enable us to determine whether a longer intervention period can generate even more favorable outcomes.

A no-cost extension of the award period has been granted through 13 August 2008. Accordingly, it is our intention to continue recruitment efforts through August 2007 and complete all follow-up evaluations of participants by June 2008. This means that, for any new participants enrolled, the period of intervention may have to be reduced by 2 mo; data analyses will adjust for the period of intervention.

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APPENDICES

none